Cortical Volume Differences in Subjects at Risk for Psychosis Are Driven by Surface Area

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Abstract: In subjects at risk for psychosis, the studies on gray matter volume (GMV) predominantly reported volume loss compared with healthy controls (CON). However, other important morphological measurements such as cortical surface area (CSA) and cortical thickness (CT) were not systematically compared. So far, samples mostly comprised subjects at genetic risk or at clinical risk fulfilling an ultra-high risk (UHR) criterion. No studies comparing UHR subjects with at-risk subjects showing only basic symptoms (BS) investigated the differences in CSA or CT. Therefore, we aimed to unravel the contribution of the 2 morphometrical measures constituting the cortical volume (CV) and to test whether these groups inhere different morphometric features. We conducted a surface-based morphometric analysis in 34 CON, 46 BS, and 39 UHR to examine between-group differences in CV, CSA, and CT vertex-wise across the whole cortex. Compared with BS and CON, UHR individuals presented increased CV in frontal and parietal regions, which was driven by larger CSA. These groups did not differ in CT. Yet, at-risk subjects who later developed schizophrenia showed thinning in the occipital cortex. Furthermore, BS presented increased CSA compared with CON. Our results suggest that volumetric differences in UHR subjects are driven by CSA while CV loss in converters seems to be based on cortical thinning. We attribute the larger CSA in UHR to aberrant pruning representing a vulnerability to develop psychotic symptoms reflected in different levels of vulnerability for BS and UHR, and cortical thinning to a presumably stress-related cortical decomposition.

DOI: https://doi.org/10.1093/schbul/sbaa066

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ABSTRACT

In subjects at risk for psychosis, studies on gray matter volume (GMV) predominantly reported volume loss compared to healthy controls (CON). However, other important morphological measurements such as cortical surface area (CSA) and cortical thickness (CT) were not systematically compared. So far, samples mostly comprised subjects at genetic risk or at clinical risk fulfilling an ultra-high risk (UHR) criterion. No studies comparing UHR subjects with at-risk subjects showing only basic symptoms (BS) investigated differences in CSA or CT. Therefore, we aimed to unravel the contribution of the two morphometrical measures constituting the CV, and to test whether these groups inhere different morphometric features.

We conducted a surface-based morphometric analysis in 34 CON, 46 BS, and 39 UHR to examine between-group differences in CV, CSA, and CT vertex-wise across the whole cortex. Compared to BS and CON, UHR individuals presented increased CV in frontal and parietal regions, which was driven by larger CSA. These groups did not differ in CT. Yet, at-risk subjects who later developed schizophrenia showed thinning in the occipital cortex. Further, BS presented increased CSA compared to CON.

Our results suggest that volumetric differences in UHR subjects are driven by CSA while CV loss in converters seems to be based on cortical thinning. We attribute the larger CSA in UHR to aberrant pruning representing a vulnerability to develop psychotic symptoms reflected in different levels of vulnerability for BS and UHR, and cortical thinning to a presumably stress-related cortical decomposition.

INTRODUCTION

There is ample evidence for morphometric brain alterations in schizophrenia, most consistently in terms of decreased gray matter volume (GMV) or gray matter density[1–3]. Studies show that already subjects at risk for psychosis present reductions of cortical GMV relative to healthy controls (CON), similarly located but less pronounced than in schizophrenia[4–8]. Studies on subjects at risk are not only advantageous because a greater proportion of the subjects is drug-naive but also because they allow to investigate the time around transition and even the (prodromal) phase prior to the transition. Criteria defining the at-risk state vary, they describe either a genetic or a clinical risk. Two common sets of criteria are used to diagnose the clinical risk: the basic symptoms (BS) criteria and the ultra-high risk (UHR) criteria. The BS consist of subtle, subclinical, self-experienced disturbances, that are experienced as dysfunctional[9,10], subsumed in two BS criteria, i.e. cognitive-perceptive BS (COPER) and cognitive-disturbances (COGDIS). This approach was developed to detect the risk for psychosis as early as possible in the development of the illness, ideally before functional impairments appeared[11]. In contrast, the UHR criteria were originally developed with the explicit aim of detecting an imminent risk for transition into a manifest psychosis within the next twelve months. An UHR criterion is met by either presenting brief, limited, intermittent psychotic symptoms (BLIPS), attenuated psychotic symptoms (APS), or alternatively meeting the state-trait criterion[12,13]. It is assumed that basic symptoms arise earlier in the course of the disease[14]. Additional APS may occur in the further course, and it is also being discussed whether APS occur in response to the basic symptoms[15].

Most imaging studies on subjects with a clinical high risk comprise UHR subjects. As BS appear to arise earlier in time course[16–18], they hold the potential to reveal processes taking place even before psychotic symptoms arise.

Morphometric studies on samples at genetic risk or at UHR commonly reported less GMV in frontal and temporal regions[19,20]. When CT in clinical risk subjects was investigated, thinning in temporal, frontal, parietal, and occipital regions was found[6]. Other studies reported negative findings in UHR[21–25] or cortical thickening in clinical[8] and genetic[26] high-risk subjects. Further, Prasad et al.[27] found decreased CSA in a genetic high-risk sample compared to CON. However, it should be considered that some studies included subjects only on the basis of the genetic risk without functional decline, which is associated with a rather low conversion rate.

Since most imaging studies on at-risk subjects are based on genetic high-risk or UHR samples, only little is known about at-risk subjects suffering from BS. Nevertheless, a voxel-based morphometry (VBM) study yielded that subjects suffering from BS showed GMV reductions in temporolimbic regions relative to CON[28]. Subjects meeting an UHR criterion additionally showed reduced GMV in prefrontal areas, enabling to distinguish the two at-risk groups[28]. The pattern of these differential neuroanatomical properties associated with different transition risks led to the interpretation of different levels of vulnerability. Further, studies applying machine learning were able to differentiate BS and UHR subjects based on anteroposterior cingulate and perisylvian areas[29] and showed different brain age gap estimations, i.e. accelerated brain age in UHR but not in BS[30]. However, these studies as well as the majority of morphometric studies in subjects at clinical risk are based on volumetric measurements. Since CV is constituted by CT and CSA[31], loss of GMV could be a result of cortical thinning, or reduced CSA, or a combination of both. Hence, any cortical

thinning in combination with extended CSA in the same region, or vice versa, cannot be detected by analyzing the GMV. Furthermore, as CSA and CT are related to different genetic[32,33] and different developmental trajectories[31], the analysis of both properties reveals distinct information and might shed light on aberrant processes involved in the pathogenesis. Reduced CT together with normal CSA – as reported in neurodegenerative diseases[34,35] – would refer to neurodegenerative pathogenetic models[36] in contrary to neurodevelopmental models of pathogenesis[37].

To the best of our knowledge, no publication investigated measures of CV, CT, and CSA comparing BS, UHR, and CON so far. Therefore, we analyzed CV, CT, and CSA in these populations and tested whether at-risk subjects fulfilling UHR criteria present morphometric differences compared to at-risk subjects meeting only BS criteria. Based on the results reported by Koutsouleris et al.[28], we hypothesized that at-risk subjects would show reductions of GMV relative to CON, specifically the UHR group more pronounced than the BS group. Further, as GMV loss in schizophrenia was found to be based on cortical thinning[38,39], we expected that GMV reductions in clinical at-risk subjects were driven by reductions of CT.

METHODS

Participants

This study was approved by the local ethics committee of the University of Zurich (KEK-Nr. E63/2009). All participants or their parents for individuals under 18 years of age signed a consent form, after they were informed about the study[40]. After excluding MRI data of inadequate quality (e.g. due to artifacts) and balancing the groups regarding age (mean±sd: 22.11±4.17, range: 16-35), sex, handedness, and IQ, 119 individuals were included in the

analyses: 46 subjects showing BS (3 with transition to schizophrenia), 39 subjects fulfilling an UHR criterion (7 with transition) and 34 CON. Since the majority of UHR subjects (35/39) also met BS criteria (supplementary text S1.4), there is a large overlap between UHR and BS which should be highlighted. Subsets of this sample (76 subjects) of which fMRI data were available were part of our previous fMRI studies[41,42].

The adult[10] respectively the children-youth[43] version of the Schizophrenia Proneness Instrument was used to assess basic symptoms. Persons included in the BS group presented either at least one out of ten cognitive-perceptive (COPER) symptoms or at least two of nine cognitive disturbances (COGDIS). UHR subjects reported at least one APS or one BLIPS, assessed by the Structured Interview for Prodromal Syndromes (SIPS)[13] (see supplementary text S1.2 for more details). Subjects fulfilling only the state-trait criteria were not included because they did not present psychotic symptoms (supplementary text S1.3). In total, 8 BS and 12 UHR subjects were being treated with second-generation (atypical) antipsychotic drugs. Within a span of 3 years (mean=12.2 months), 10 individuals developed schizophrenia (Table 1, supplementary text S1.5.2 for individual time to transition).

The CON group has been recruited through advertisements. To ensure that this group did not include subjects with an ongoing or preceding psychiatric illness, the Mini-International Neuropsychiatric Interview[44] was conducted. Exclusion criteria for all participants were contraindications against MRI, pregnancy, history of neurological disease, and drug/alcohol dependence. Further, subjects holding organic brain anomalies (supplementary text S1.1) were excluded from the study (n=14), as verified by an experienced neuroradiologist.

In order to balance the three groups regarding IQ and handedness (Table 1), levels of intelligence were estimated[45] in adults with a German test for word recognition

(Mehrfachwahl Wortschatz Test, Version B; MWT-B)[46] and in adolescent subjects (age <20) by using a test for fluid non-verbal intelligence (Leistungsprüfsystem, subtest 3, LPS-3)[47]. Handedness was ascertained by the Edinburg Handedness Inventory[48].

INSERT_TABLE_1_HERE

Image Acquisition and Processing

Magnetic resonance imaging (MRI) was applied to acquire three-dimensional T1-weighted structural images of the whole brain. Data were obtained on a Philips Achieva TX 3-T whole-body MR unit, using an 8-channel head coil and a fast field echo pulse sequence (repetition time, TR=8.3ms, echo time, TE=3.8ms, flip-angle 8 degree, field of view, FOV 240x240mm^2, voxel size 1x1x1mm^3 (reconstructed: 0.94x0.94x1mm^3), 160 contiguous slices. Images with obvious artifacts (e.g., caused by head motion or dental braces) were excluded from the study (n=4). All datasets were processed on the same workstation using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). The automated processing stream enables to extract reliable estimates of cortical anatomic measures. The procedure included several steps: intensity normalization, skull-stripping, Talairach transformation, and atlas-based assignment of neuro-anatomical labels, as previously described[49]. The generated models of the cortical surfaces, defined by the white/gray boundary and gray/cerebrospinal fluid boundary, allowed to calculate CT (representing the closest distance between white and pial surfaces), CSA as well as the product of CT and CSA (representing CV). These morphometric features were calculated at each vertex across the whole cortex. Generated models were visually inspected for each subject, and data was excluded from the study in case the visual inspection revealed errors (n=9). Finally, data

were smoothed by applying a surface-based smoothing kernel with a full width at half maximum of about 10 mm.

Statistical Analysis

In order to assure a balanced distribution between groups with respect to age and IQ as well as sex and handedness, we performed statistical tests using the R 3.2.3 software (R Core Team, 2015): One-way analyses of variances (ANOVAs) or chi-square tests were applied. In case Shapiro-Wilk test for normality revealed that the dependent variable was not normally distributed, Kruskal-Wallis test instead of ANOVA was performed. The same was done for analyses on global hemispheric brain measures, i.e. total CV, mean CT, and total CSA per hemisphere.

Vertex-wise analyses on morphometric measures were conducted with FreeSurfer software 5.3.0 (http://surfer.nmr.mgh.harvard.edu). To test for differences across groups, we fitted a general linear model at each vertex across the cortex, with CV, CT, and CSA, respectively, as dependent variables. Since groups are balanced regarding age, sex, IQ and handedness, we did not include these variables. F-tests were performed to identify whether there are differences between any of the three groups. In case of a significant main effect post-hoc T-tests comparing BS versus UHR, BS versus CON, and UHR versus CON were conducted separately. We further investigated subgroups of at-risk groups, defined by the clinical outcome, i.e. 10 at-risk subjects with transition (RISK-T) to schizophrenia (F20 according to ICD-10[50]) versus those without transition (RISK-NT). Subjects with transition to other diseases than schizophrenia were not included in this additional analysis, predominantly to increase the homogeneity of the RISK-T sample (supplementary text S1.5.1). Further, Spearman's correlation was used to examine the association between morphometric

measures and symptoms (SIPS positive score, COPER and COGDIS sum scores, Tables S2.3.1-S2.3.3, Fig. S2.6.1-S2.6.4).

Cortical surfaces of both hemispheres were analyzed separately. To correct for multiple comparisons, Monte Carlo simulations were performed (10,000 iterations) with a cluster-wise threshold of $p<.05$ (two-tailed). Results were displayed on the average brain based on the subjects of our study sample.

Some at-risk subjects were treated with antipsychotic medication (Table 1), which are known to inhere the potential to induce morphological changes on gray matter[51]. We thus performed an additional analysis controlled for CPZ equivalents (supplementary material S2.2).

RESULTS

Demographic and clinical characteristics

The three groups were balanced regarding age ($p=.5111$), sex ($p=.2789$), handedness ($p=.2659$) and IQ ($p=.1034$). Significant between-group differences were found in COPER sum score ($p<.0216$), SIPS positive score ($p<.0001$), SIPS disorganization ($p<.0001$), SIPS general ($p<.0197$) and global functioning (GAF, $p=.0087$) between the BS and UHR groups. In contrast, these two groups did not differ regarding COGDIS sum score ($p=.1014$), SIPS negative score ($p=.0675$), and neither in CPZ equivalents ($p=.1706$), see Table 1 for more details.

Global hemispheric measurements

ANOVAs for total CV, total CSA and mean CT in each hemisphere among the CON, BS, and UHR groups did not yield significant differences (Table S2.1.1).

Vertex-wise cortical volume (CV)

ANOVA among the three groups revealed significant group differences (Table S2.1.2): UHR showed greater GMV than BS in the left lateral orbitofrontal (p=.0001, Monte Carlo simulation), and right posterior cingulate cortex (p=.0064, Monte Carlo simulation), and relative to CON in a right inferior parietal region (p=.0224, Monte Carlo simulation) and the right precuneus (p=.0445, Monte Carlo simulation), see Fig. 1.

Vertex-wise cortical surface area (CSA)

Group effects were significant among the three groups (Table S2.1.2). A larger CSA was seen in UHR compared to BS in a left lateral orbitofrontal region (p=.0007, Monte Carlo simulation) as well as in the right posterior cingulate cortex (p=.0107, Monte Carlo simulation) as shown in Fig. 1. UHR also demonstrated larger CSA when compared to CON in left orbitofrontal and lateral occipital cortex (p=.0469, Monte Carlo simulation and p=.0006, Monte Carlo simulation, respectively), and in the right superior parietal cortex (p=.0001, Monte Carlo simulation). BS showed larger CSA relative to CON in the left inferior temporal cortex (p=.04, Monte Carlo simulation).

Vertex-wise cortical thickness (CT)

No cluster of significant group differences in CT survived the correction for multiple comparisons.

INSERT_FIGURE_1_HERE

Transition to psychosis

RISK-T showed reduced CV in the left and right lateral occipital cortex (left: p =.0104, right: p=.0038, Monte Carlo simulation) and thinning in the left lateral occipital cortex (p=.0005, Monte Carlo simulation) when compared to RISK-NT (Fig. 2, Table S2.1.3). Compared to CON, RISK-T differed in CT in the left lateral occipital cortex (p=.0018, Monte Carlo simulation) and the right cuneus (p=.0037, Monte Carlo simulation). RISK-NT showed larger CSA in the left inferior temporal cortex (p=.0256, Monte Carlo simulation) compared to CON.

INSERT_FIGURE_2_HERE

Controlled for CPZ equivalents

When controlling for CPZ equivalents, the results did not substantially dissent from the results without regressing out CPZ equivalents (Fig. S2.2.1/S2.2.2, Table S2.2.1).

Correlation with symptoms

The clusters showing increased CSA in UHR are not significantly correlated with positive symptoms, neither the cluster with cortical thinning in the left lateral occipital cortex in RISK-T (Table S2.3.1). These clusters do not correlate with the COPER sum score (Table S2.3.2) or the COGDIS sum score (Table S2.3.3) either.

DISCUSSION

Our study aimed to unravel how CV relies on CSA and CT in subjects fulfilling BS and UHR criteria and to test whether these two groups can be differentiated from each other and

from CON in regard to their morphometric measures. We observed increased CV in UHR subjects in the cingulate cortex and in frontal regions relative to BS and in frontal, parietal and occipital regions compared to CON. These differences were produced by larger CSA. Further, BS showed increased CSA in a left temporal area when compared to CON. No alterations in CT were found in the UHR and BS groups but RISK-T presented cortical thinning in the lateral occipital cortex at baseline relative to RISK-NT.

According to the radial unit hypothesis[52], CSA is determined by the number of cortical columns, whereas CT is based on the number of neurons within a column[52,53]. The two components are driven by different genetic mechanisms[32,33], and also different developmental influences. A study investigating the cortical development in early childhood reported that CT is developed earlier than CSA: By age two, CT is 97% of adult values, CSA only 69%. The authors concluded that cortical growth after age 1 is mainly induced by increases in CSA[54].

The CV differences between UHR subjects and BS/CON in our sample were driven by differences in CSA. Hence, CV differences driven by CSA between UHR and CON might indicate that developmental processes which determine cortical growth are affected in UHR subjects. These alterations might occur either in cell migration[55] early in development (pre-/perinatal), or in later processes which normally reduce CSA in development (i.e., pruning)[56]. We suggest that later processes, which are supposed to reduce the surface, might be affected because the CSA in UHR is larger than in CON. This assumption is supported by a study reporting fewer reductions longitudinally within two years in global CSA in genetic high-risk subjects aged 16-27 years when compared to CON.

Altered maturation could be based on aberrant synaptic plasticity which is hypothesized to cause changes in perceptual or reinforcement learning potentially resulting in neurocognitive aberrations, delusions and hallucinations[57,58]. We suppose that aberrant synaptic plasticity might lead to changes in pruning due to strengthening of "atypical" synaptic connections which will consequently be reflected in increased regional CSA. This might explain why the orbitofrontal cortex, a region involved in reinforcement learning[59] showed increased CSA in UHR.

Therefore, we suggest that increased CSA in UHR subjects might reflect aberrant or delayed pruning. It is also conceivable, that increased CSA occurs due to insufficient (or delayed) intracortical myelination[60]. Reduced myelination in schizophrenic patients support this suggestion[61], as well as post-mortem and genomic studies, summarized in Palaniyappan et al.[60]. Whether it might be reduced pruning or reduced myelination cannot be revealed with our data, but either explanation might represent a sign of delayed maturation[62]. This could also explain why the morphometric changes are not correlated with the symptoms.

Alternatively, the increase of CSA might be caused by cortical reorganization: Taking into consideration that UHR-symptoms are thought to develop from basic symptoms[63] or eventually arise in response to them, and the majority of UHR subjects in our sample also presents basic symptoms, the increased CSA might reflect these compensational processes, also discussed as indicator of resilience[60]. Yet, CSA increases did not correlate with symptoms. This might be a hint that these changes are related to the development rather than to a putative compensation[8,60].

Regarding CT differences, our negative finding is in line with studies showing no or only subtle morphometric differences in at-risk subjects[22,24]. Yet, cortical thinning without

differences in CV and CSA has been reported in converters[64]. Accordingly, our analyses revealed occipital cortices to be thinner in converters. Hence, transition to psychosis appears to be associated with decreased CT. This assumption is in line with studies concluding that CV loss in schizophrenia patients is driven by cortical thinning[38,39]. In contrast, Bois et al.[65] found that in their genetic at-risk sample increased CSA is related to the transition while cortical thinning was not associated with the subsequent clinical outcome. Here, the questions about the time point of appearance and the causes of alterations in CT arise. One study revealed differences very early in development: In their preliminary study, Li et al.[66] found smaller (along with increased) CT in genetic high-risk neonates, indicating that differences in CT in the sense of a reduced cortical growth might arise already around time birth. Yet, these preliminary results originate from region of interest (ROI)-based analyses, most of the differences were only detected without correction for multiple comparisons and the majority of the reported anomalies were located in different regions from those in our sample, and above all, it was a genetic high-risk sample. Given the cortical thinning we found did not arise around time birth, but later as a decomposition of the cortex, there is evidence suggesting that a thinner cortex might result from microglial anomalies[67,68], referring to inflammatory processes. Further, Cannon et al.[24] found the rate of prefrontal cortical thinning to be predicted by proinflammatory markers at baseline with stronger association in subjects who subsequently developed psychosis. Remarkably, neither the levels of these markers nor CT at baseline did differ between groups. It is still not known whether these microglial alterations are causative or not. Cortical thinning (also the possibly inflammatory processes) could represent a consequence of stress, caused by increasing and persisting symptoms. It is well established that repeated or chronic stress provokes morphological changes in the brain, e.g. in the

hippocampus but also in prefrontal cortical areas[69], notably structures demonstrating CV loss and cortical thinning in schizophrenia as well as in at-risk subjects[4,70]. Hence, cortical thinning might be rather related to stress than to the transition itself.

Our findings indicate that CV differences driven by CSA might be caused by aberrant developmental processes (presumably deficient/delayed pruning) and could represent the basis for the increased vulnerability to develop psychotic symptoms. In contrast, cortical thinning, probably related to pubertal stressors and stress provoked by arising symptoms, might drive the volume loss detected in at-risk samples with a high percentage of converters and later on in schizophrenia – more pronounced by the persisting symptoms and their increasing severity. This assumption is corroborated by the findings of a study[71] analyzing the anterior cingulate gyrus: increased CSA in UHR subjects relative to CON but cortical thinning in converters. This would partially explain the discrepancies of findings in the literature: As morphometric differences increase from the at-risk state to psychosis, different transition rates are likely to be associated with differently pronounced morphometric alterations, particularly cortical thinning resulting in loss of GMV. Correspondingly, the relatively low transition rate in our sample (13%), is associated with less GMV reductions than found in other studies with a higher rate of transition. The higher transition rate (45%) in the study of Koutsouleris et al.[28] might be the basis for the revealed GMV loss in the early and the late at risk mental state (ARMS-E and ARMS-L, corresponding to the BS and UHR groups respectively) and partially explain the discrepancies to our results.

Limitations

When interpreting our results, it has to be taken into account that some at-risk subjects were treated with antipsychotic medication (Table 1), which are known to inhere the potential to induce morphological changes on gray matter[51,72]. We thus performed additional analyses controlling for CPZ equivalents. The results (Fig. S2.2.1/S2.2.2) did not dissent substantially from the presented results without including CPZ equivalents as a nuisance variable, hence, the presented differences cannot be attributed to the antipsychotic treatment. Further, the cross-sectional study design does not allow to directly draw conclusions about the developmental trajectories of the gray matter morphology.

Conclusion

Our results indicate that CV differences in UHR subjects are driven by CSA and not by CT. In contrast, CV loss in converters is related to cortical thinning. We conclude that increased CSA might result from aberrant or delayed pruning owed to a neurodevelopmental delay. We consider the increased CSA to represent a predisposition for psychotic symptoms more pronounced in UHR than in subjects with only BS reflecting different risk-levels for transition. On the other hand, cortical thinning might be associated with elevated stress-levels induced by aggravated symptoms during the onset of manifest schizophrenia.

Funding

This work was supported by the Zurich Program for Sustainable Development of Mental Health Services (ZInEP). The donor had no further role in the experimental design, collection, analysis, interpretation of data, writing, and submitting this paper for publication.

Acknowledgements

The authors would like to thank the psychiatrists and psychologists of the ZInEP team for assisting with data collection, all subjects and their families for their participation, and the ZInEP for funding.

Conflict of interest

Dr. Rössler has served as a consultant or received honoraria from Eli Lilly Suisse, Janssen-Cilag, Interpharma, FOMF, Med-Update, SVA Sozialversicherungsanstalt Schweiz, I3G, and IVP Networks during the last 5 years. Dr. Walitza has received lecture honoraria from AstraZeneca, Eli Lilly, Opopharma and Janssen Cilag in the last five years.

Figure 1

Morphometric differences between the three study groups. The three post-hoc tests comprise the comparisons of at-risk subjects showing only basic symptoms (BS), subjects at ultra-high risk (UHR), and healthy controls (CON). Blue highlighting indicates areas with larger ($p<.05$, two-tailed, Monte Carlo simulations) cortical volume and surface area, respectively, in the second group of the comparison.

Figure 2

Morphometric differences between at-risk subjects who later developed psychosis (RISK-T) and those who did not (RISK-NT). Red/yellow delineates areas with smaller ($p<.05$, two-tailed, Monte Carlo simulations) volume and cortical thickness, respectively, in the second group of the comparison.

References

1. Fornito A, Yücel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophr Res* 2009;108(1-3):104-113. doi:10.1016/j.schres.2008.12.011.

2. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev* 2013;37(8):1680-1691. doi:10.1016/j.neubiorev.2013.06.001.

3. Zhao C, Zhu J, Liu X, et al. Structural and functional brain abnormalities in schizophrenia: A cross-sectional study at different stages of the disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;83:27-32. doi:10.1016/j.pnpbp.2017.12.017.

4. Fusar-Poli P, Radua J, McGuire P, Borgwardt S. Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies. *Schizophr Bull* 2012;38(6):1297-1307. doi:10.1093/schbul/sbr134.

5. Chang M, Womer FY, Bai C, et al. Voxel-Based Morphometry in Individuals at Genetic High Risk for Schizophrenia and Patients with Schizophrenia during Their First Episode of Psychosis. *PLoS ONE* 2016;11(10):e0163749. doi:10.1371/journal.pone.0163749.

6. Jung WH, Kim JS, Jang JH, et al. Cortical thickness reduction in individuals at ultra-high-risk for psychosis. *Schizophr Bull* 2011;37(4):839-849. doi:10.1093/schbul/sbp151.

7. Borgwardt S, McGuire P, Fusar-Poli P. Gray matters!--mapping the transition to psychosis. *Schizophr Res* 2011;133(1-3):63-67. doi:10.1016/j.schres.2011.08.021.

8. Dukart J, Smieskova R, Harrisberger F, et al. Age-related brain structural alterations as an intermediate phenotype of psychosis. *J Psychiatry Neurosci* 2017;42(5):307-319. doi:10.1503/jpn.160179.

9. Schultze-Lutter F, Schimmelmann BG, Ruhrmann S. The near Babylonian speech confusion in early detection of psychosis. *Schizophr Bull* 2011;37(4):653-655. doi:10.1093/schbul/sbr039.

10. Schultze-Lutter F, Addington J, Ruhrmann S, Klosterkötter J. *Schizophrenia Proneness Instrument, Adult Version (SPI-A)*. (Editore s.r.l. GF, ed.). Rome, Italy; 2007.

11. Schultze-Lutter F, Michel C, Schmidt SJ, et al. EPA guidance on the early detection of

clinical high risk states of psychoses. *Eur Psychiatry* 2015;30(3):405-416. doi:10.1016/j.eurpsy.2015.01.010.

12. Yung AR, Phillips LJ, McGorry PD, et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl* 1998;172(33):14-20.

13. McGlashan T, Miller TJ, Woods SW, Rosen JL, Hoffman RE, Davidson L. *Structured Interview for Prodromal Syndromes - Version for Present Prodromal Syndromes.* New Haven, Connecticut: PRIME Research Clinic, Yale School of Medicine; 2001.

14. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA psychiatry* 2013;70(1):107-120. doi:10.1001/jamapsychiatry.2013.269.

15. Cascio N Lo, Saba R, Hauser M, et al. Attenuated psychotic and basic symptom characteristics in adolescents with ultra-high risk criteria for psychosis, other non-psychotic psychiatric disorders and early-onset psychosis. *Eur Child Adolesc Psychiatry* 2016;25(10):1091-1102. doi:10.1007/s00787-016-0832-7.

16. Schultze-Lutter F, Ruhrmann S, Berning J, Maier W, Klosterkötter J. Basic symptoms and ultrahigh risk criteria: symptom development in the initial prodromal state. *Schizophr Bull* 2010;36(1):182-191. doi:10.1093/schbul/sbn072.

17. Häfner H, Maurer K, Ruhrmann S, et al. Early detection and secondary prevention of psychosis: facts and visions. *Eur Arch Psychiatry Clin Neurosci* 2004;254(2):117-128. doi:10.1007/s00406-004-0508-z.

18. Ruhrmann S, Schultze-Lutter F, Klosterkötter J. Early detection and intervention in the initial prodromal phase of schizophrenia. *Pharmacopsychiatry* 2003;36 Suppl 3:S162-7. doi:10.1055/s-2003-45125.

19. Thermenos HW, Keshavan MS, Juelich RJ, et al. A review of neuroimaging studies of young relatives of individuals with schizophrenia: a developmental perspective from schizotaxia to schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2013;162B(7):604-635. doi:10.1002/ajmg.b.32170.

20. Jung WH, Borgwardt S, Fusar-Poli P, Kwon JS. Gray matter volumetric abnormalities associated with the onset of psychosis. *Front Psychiatry* 2012;3:101.

21. Haller S, Borgwardt SJ, Schindler C, Aston J, Radue EW, Riecher-Rössler A. Can cortical thickness asymmetry analysis contribute to detection of at-risk mental state and first-episode psychosis? A pilot study. *Radiology* 2009;250(1):212-221. doi:10.1148/radiol.2501072153.

22. Klauser P, Zhou J, Lim JKW, et al. Lack of evidence for regional brain volume or cortical thickness abnormalities in youths at clinical high risk for psychosis: findings from the longitudinal youth at risk study. *Schizophr Bull* 2015;41(6):1285-1293.

doi:10.1093/schbul/sbv012.

23. Ziermans TB, Schothorst PF, Schnack HG, et al. Progressive structural brain changes during development of psychosis. *Schizophr Bull* 2012;38(3):519-530. doi:10.1093/schbul/sbq113.

24. Cannon TD, Chung Y, He G, et al. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry* 2015;77(2):147-157. doi:10.1016/j.biopsych.2014.05.023.

25. Sakuma A, Obara C, Katsura M, et al. No regional gray matter volume reduction observed in young Japanese people at ultra-high risk for psychosis: A voxel-based morphometry study. *Asian J Psychiatr* 2018;37:167-171. doi:10.1016/j.ajp.2018.09.009.

26. Li X, Alapati V, Jackson C, et al. Structural abnormalities in language circuits in genetic high-risk subjects and schizophrenia patients. *Psychiatry Res* 2012;201(3):182-189. doi:10.1016/j.pscychresns.2011.07.017.

27. Prasad KM, Goradia D, Eack S, et al. Cortical surface characteristics among offspring of schizophrenia subjects. *Schizophr Res* 2010;116(2-3):143-151. doi:10.1016/j.schres.2009.11.003.

28. Koutsouleris N, Schmitt GJE, Gaser C, et al. Neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes. *Br J Psychiatry* 2009;195(3):218-226. doi:10.1192/bjp.bp.108.052068.

29. Koutsouleris N, Gaser C, Bottlender R, et al. Use of neuroanatomical pattern regression to predict the structural brain dynamics of vulnerability and transition to psychosis. *Schizophr Res* 2010;123(2-3):175-187. doi:10.1016/j.schres.2010.08.032.

30. Koutsouleris N, Davatzikos C, Borgwardt S, et al. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. *Schizophr Bull* 2014;40(5):1140-1153. doi:10.1093/schbul/sbt142.

31. Wierenga LM, Langen M, Oranje B, Durston S. Unique developmental trajectories of cortical thickness and surface area. *Neuroimage* 2014;87:120-126. doi:10.1016/j.neuroimage.2013.11.010.

32. Chen C-H, Fiecas M, Gutiérrez ED, et al. Genetic topography of brain morphology. *Proc Natl Acad Sci U S A* 2013;110(42):17089-17094. doi:10.1073/pnas.1308091110.

33. Panizzon MS, Fennema-Notestine C, Eyler LT, et al. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex* 2009;19(11):2728-2735. doi:10.1093/cercor/bhp026.

34. Dickerson BC, Feczko E, Augustinack JC, et al. Differential effects of aging and

Alzheimer's disease on medial temporal lobe cortical thickness and surface area. *Neurobiol Aging* 2009;30(3):432-440. doi:10.1016/j.neurobiolaging.2007.07.022.

35. Nygaard GO, Walhovd KB, Sowa P, et al. Cortical thickness and surface area relate to specific symptoms in early relapsing-remitting multiple sclerosis. *Mult Scler* 2015;21(4):402-414. doi:10.1177/1352458514543811.

36. DeLisi LE. Is schizophrenia a lifetime disorder of brain plasticity, growth and aging? *Schizophr Res* 1997;23(2):119-129. doi:10.1016/S0920-9964(96)00079-5.

37. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res* 1982;17(4):319-334. doi:10.1016/0022-3956(82)90038-3.

38. Rimol LM, Nesvåg R, Hagler DJ, et al. Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biol Psychiatry* 2012;71(6):552-560. doi:10.1016/j.biopsych.2011.11.026.

39. Benetti S, Pettersson-Yeo W, Hutton C, et al. Elucidating neuroanatomical alterations in the at risk mental state and first episode psychosis: a combined voxel-based morphometry and voxel-based cortical thickness study. *Schizophr Res* 2013;150(2-3):505-511. doi:10.1016/j.schres.2013.08.030.

40. Theodoridou A, Heekeren K, Dvorsky D, et al. Early recognition of high risk of bipolar disorder and psychosis: an overview of the zinep "early recognition" study. *Front Public Health* 2014;2:166. doi:10.3389/fpubh.2014.00166.

41. Wotruba D, Michels L, Buechler R, et al. Aberrant coupling within and across the default mode, task-positive, and salience network in subjects at risk for psychosis. *Schizophr Bull* 2014;40(5):1095-1104. doi:10.1093/schbul/sbt161.

42. Wotruba D, Heekeren K, Michels L, et al. Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis. *Front Behav Neurosci* 2014;8:382. doi:10.3389/fnbeh.2014.00382.

43. Schultze-Lutter F, Koch E. *Schizophrenia Proneness Instrument, Child and Youth Version (SPI-CY)*. Rome, Italy: Giovanni Fioriti Editore; 2010.

44. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 Suppl 20:22-33.

45. Metzler S, Dvorsky D, Wyss C, et al. Neurocognitive profiles in help-seeking individuals: comparison of risk for psychosis and bipolar disorder criteria. *Psychol Med* 2014;44(16):3543-3555. doi:10.1017/S0033291714001007.

46. Lehrl S. *Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B*. Balingen: Spitta Verlag; 1999.

47. Horn W. *L-P-S Leistungsprüfsystem*. 2nd ed. Göttingen: Verlag für Psychologie, Hogrefe; 1983.

48. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9(1):97-113. doi:10.1016/0028-3932(71)90067-4.

49. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* 1998;17(1):87-97. doi:10.1109/42.668698.

50. Organization WH. *The Icd-10 Classification Of Mental And Behavioural Disorders: Clinical Descriptions And Diagnostic Guidelines*. 1st ed. Geneva: World Health Organization; 1992:374.

51. Vita A, De Peri L, Deste G, Barlati S, Sacchetti E. The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-analysis and Meta-regression of Longitudinal Magnetic Resonance Imaging Studies. *Biol Psychiatry* 2015;78(6):403-412. doi:10.1016/j.biopsych.2015.02.008.

52. Rakic P. Specification of cerebral cortical areas. *Science* 1988;241(4862):170-176. doi:10.1126/science.3291116.

53. Pontious A, Kowalczyk T, Englund C, Hevner RF. Role of intermediate progenitor cells in cerebral cortex development. *Dev Neurosci* 2008;30(1-3):24-32. doi:10.1159/000109848.

54. Lyall AE, Shi F, Geng X, et al. Dynamic development of regional cortical thickness and surface area in early childhood. *Cereb Cortex* 2015;25(8):2204-2212. doi:10.1093/cercor/bhu027.

55. Muraki K, Tanigaki K. Neuronal migration abnormalities and its possible implications for schizophrenia. *Front Neurosci* 2015;9:74. doi:10.3389/fnins.2015.00074.

56. Schnack HG, van Haren NEM, Brouwer RM, et al. Changes in thickness and surface area of the human cortex and their relationship with intelligence. *Cereb Cortex* 2015;25(6):1608-1617. doi:10.1093/cercor/bht357.

57. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. *Biol Psychiatry* 2006;59(10):929-939. doi:10.1016/j.biopsych.2005.10.005.

58. Huys QJM, Guitart-Masip M, Dolan RJ, Dayan P. Decision-Theoretic Psychiatry. *Clinical Psychological Science* 2015;3(3):400-421. doi:10.1177/2167702614562040.

59. Frank MJ. Schizophrenia: a computational reinforcement learning perspective. *Schizophr Bull* 2008;34(6):1008-1011. doi:10.1093/schbul/sbn123.

60. Palaniyappan L, Das T, Dempster K. The neurobiology of transition to psychosis: clearing the cache. *J Psychiatry Neurosci* 2017;42(5):294-299. doi:10.1503/jpn.170137.

61. Palaniyappan L, Al-Radaideh A, Mougin O, Gowland P, Liddle PF. Combined white matter imaging suggests myelination defects in visual processing regions in schizophrenia. *Neuropsychopharmacology* 2013;38(9):1808-1815. doi:10.1038/npp.2013.80.

62. Catts VS, Fung SJ, Long LE, et al. Rethinking schizophrenia in the context of normal neurodevelopment. *Front Cell Neurosci* 2013;7:60. doi:10.3389/fncel.2013.00060.

63. Jimeno N, Gomez-Pilar J, Poza J, et al. Main symptomatic treatment targets in suspected and early psychosis: new insights from network analysis. *Schizophr Bull* 2020. doi:10.1093/schbul/sbz140.

64. Fornito A, Yung AR, Wood SJ, et al. Anatomic abnormalities of the anterior cingulate cortex before psychosis onset: an MRI study of ultra-high-risk individuals. *Biol Psychiatry* 2008;64(9):758-765. doi:10.1016/j.biopsych.2008.05.032.

65. Bois C, Ronan L, Levita L, et al. Cortical surface area differentiates familial high risk individuals who go on to develop schizophrenia. *Biol Psychiatry* 2015;78(6):413-420. doi:10.1016/j.biopsych.2014.12.030.

66. Li G, Wang L, Shi F, et al. Cortical thickness and surface area in neonates at high risk for schizophrenia. *Brain Struct Funct* 2016;221(1):447-461. doi:10.1007/s00429-014-0917-3.

67. Frick LR, Williams K, Pittenger C. Microglial dysregulation in psychiatric disease. *Clin Dev Immunol* 2013;2013:608654. doi:10.1155/2013/608654.

68. Meyer U. Developmental neuroinflammation and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2013;42:20-34. doi:10.1016/j.pnpbp.2011.11.003.

69. McEwen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. *Annu Rev Med* 2011;62:431-445. doi:10.1146/annurev-med-052209-100430.

70. Fusar-Poli P, Borgwardt S, Crescini A, et al. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neurosci Biobehav Rev* 2011;35(5):1175-1185. doi:10.1016/j.neubiorev.2010.12.005.

71. Takayanagi Y, Kulason S, Sasabayashi D, et al. Reduced Thickness of the Anterior Cingulate Cortex in Individuals With an At-Risk Mental State Who Later Develop

Psychosis. *Schizophr Bull* 2017;43(4):907-913. doi:10.1093/schbul/sbw167.

72. Smieskova R, Fusar-Poli P, Allen P, et al. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia?--a systematic review. *Curr Pharm Des* 2009;15(22):2535-2549.

SUPPLEMENTARY MATERIAL

Volume Differences in Subjects at Risk for Psychosis Are Driven by Surface Area

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S1 SUPPLEMENTARY METHODS AND PARTICIPANTS

S1.1 Exclusion due to organic brain anomalies

All MRI data were assessed by an experienced neuroradiologist. Each subject had previously given his/her consent for this clinical assessment. The neuroradiologist had no information about the group allocation of the subjects. The decision he made about exclusion due to brain changes was therefore independent of the group assignment.

These subjects stemmed from the following groups and have been excluded due to the following organic brain anomalies:

CON group:	Cavernoma (1 subject), arachnoidal cyst (1), lesions (2), increased ventricles (2)
BS group:	Pineal cyst (1), perivascular lesions (1), multiple subcortical lesions (2)
UHR group:	Demyelination (2), vascular lesions (1), perivascular lesions (1)

S1.2 Clinical assessments

All investigators who conducted psychopathological assessments received extensive training and were either psychologists or psychiatrists. In subjects at risk (BS and UHR groups), psychopathological data was gathered with the Schizophrenia Proneness Instrument-adult [1], and -child and youth Version (SPI-CY, SPI-A) [1; 2], the Structured Interview for Prodromal Syndromes (SIPS) [3; 4], the Positive and Negative Syndrome Scale (PANSS) [5], Hypomania Checklist (HCL-32) [6], Calgary Depression Scale [7], Hamilton Depression Scale (HAMD) [8], and Beck Anxiety Inventory (BAI) [9].

Subjects belonging to the CON group were assessed using the the Mini-International Neuropsychiatric Interview [10], those CON subjects who showed a preceding or ongoing psychiatric illness were excluded from the study. Since the control group was not explicitly examined for psychosis risk criteria, it cannot be completely excluded that individual persons from the control group also met the risk criteria. However, the probability is to be considered low, since the control subjects were not persons seeking help and all those with current or past substance use have been excluded.

S1.3 UHR group: state-trait criteria

According to McGlashan et al. [11], the state-trait criteria (genetic risk and deterioration syndrome, GRD) are one of the UHR approaches. As subjects fulfilling only the state-trait criteria are not presenting psychotic symptoms, a reviewer suggested to exclude these subjects. Hence, four subjects who only met the state-trait criteria were excluded from the analyses. Consequently, each UHR subject in this study presented psychotic symptoms as characterized in APS or BLIPS. However, the results with and without these four subjects fulfilling only the state-trait criteria were almost the same.

S1.4 Clinical criteria met in BS and UHR groups

BS group

46 subjects whereof ...

- 31 subjects fulfill COPER & COGDIS
- 14 subjects fulfill COPER
- 1 subject fulfills COGDIS

UHR group

39 subjects whereof ...

- 39 fulfill UHR criteria:
  - 1 subject fulfills APS & BLIPS
  - 35 subjects fulfill APS
  - 3 subjects fulfill BLIPS
- 35 (additionally) fulfill BS criteria:
  - 24 subjects COPER & COGDIS
  - 8 subjects COPER
  - 3 subjects COGDIS

S1.5 Transition (RISK-T group)

S1.5.1 Exclusion due to transition into F23 and Bipolar I disorder

As indicated in Table 1 of the article, four subjects of the RISK groups (BS and UHR) subsequently developed a frank psychotic disorder different from schizophrenia (according to ICD-10 [12]):

BS group: 2 subjects developed F23 (acute and transient psychotic disorders)

UHR group: 1 subject developed F23
1 subject developed Bipolar I disorder

Since the prediction of the transition into a manifest schizophrenic disease according to ICD-10 [12] was defined as target parameter already during the planning of our ZInEP study [13], our aim was to identify those individuals who have a severe course of the disease and a high symptom burden. Although the three transitions to F23 had a severe symptom burden over a transient period, their symptoms were completely remitted after a few weeks as required by the ICD-10 [12] criteria. Therefore, we decided not to include the three transitions to F23 as converters in the analyses.

Regarding the transition to bipolar disorder: There is evidence for neurobiological differences between schizophrenia and bipolar disorder found on the structural [14] and the functional level [15] and also prior to the onset [16] (although this study is investigating subjects with a familial risk of psychosis). Hence, we decided to restrict the analysis related to transition to schizophrenia aiming to increase the homogeneity of this subsample (RISK-T). These four subjects with transition to non-schizophrenia psychosis were not included in the RISK-NT group either because these subjects cannot be considered resilient due to their transition to a mental disease.

Consequently, the RISK-T group comprised only subjects with transition to schizophrenia according to ICD-10 [12] criteria.

S1.5.2 Time to transition (RISK-T)

Time (in months) to transition into schizophrenia for the ten RISK-T subjects: 2, 3, 4, 6, 7, 9, 13, 17, 28, 33
(3-year follow-up, mean = 12.2 months)

S2 SUPPLEMENTARY RESULTS

S2.1 Significant clusters

Table S2.1.1: Results of global measurements

Global measurements per hemisphere

Measurement	Hemisphere	Test	F/χ^2	P
CON, BS, and UHR				
Total volume	left	Kruskal-Wallis	2.8985	0.2347
	right	Kruskal-Wallis	2.369	0.3059
Total surface area	left	Kruskal-Wallis	3.6703	0.1596
	right	ANOVA	1.844	0.163
Mean thickness	left	ANOVA	1.171	0.314
	right	Kruskal-Wallis	2.1771	0.3367

Vertex-wise tests

Measurement	Hemisphere	CWP	Effect Size Cohen's d	Cluster Size (mm^2)	Number of Vertices	MNI coordinates x	y	z	Structure
Posthoc t-tests									
BS vs. UHR									
Volume	left	0.00010	−0.81	3947.83	4709	−22.5	33.9	−10.2	lateral orbitofrontal
	right	0.00640	−0.91	1338.24	2805	6.5	−7.7	38.7	posterior cingulate
Surface area	left	0.00070	−0.75	2141.54	2614	−10.1	11.3	−14.9	orbitofrontal
	right	0.01070	−0.84	1439.94	3066	7.1	−7.0	39.0	posterior cingulate
Thickness	left	n.s.							
	right	n.s.							
CON vs. BS									
Volume	left	n.s.							
	right	n.s.							
Surface area	left	0.04000	−0.72	1180.72	1515	−38.1	−9.3	−42.4	inferior temporal
	right	n.s.							
Thickness	left	n.s.							
	right	n.s.							
CON vs. UHR									
Volume	left	n.s.							
	right	0.02240	−0.94	1130.42	2351	45.6	−56.6	44.0	inferior parietal
		0.04450	−0.89	997.99	1983	8.1	−55.6	44.7	precuneus
Surface area	left	0.04690	−0.84	1143.01	1609	−11.1	14.9	−13.4	orbitofrontal
		0.00060	−0.79	1891.89	2268	−25.2	−87.4	5.1	lateral occipital
	right	0.00010	−1.09	3118.55	6533	33.2	−36.1	38.3	superior parietal
Thickness	left	n.s.							
	right	n.s.							

Table S2.1.3: Clusters of morphological differences in transition (RISK-T) and non-transition (RISK-NT)

Vertex-wise tests according to the clinical outcome: transition (Risk-T) and non-transition (Risk-NT)

Measurement	Hemisphere	CWP	Effect Size Cohen's d	Cluster Size (mm^2)	Number of Vertices	MNI coordinates			Structure
						x	y	z	
Posthoc t-tests									
RISK-NT vs. RISK-T									
Volume	left	0.01040	1.12	1262.51	1610	−19.1	−95.9	−17.4	lateral occipital
	right	0.00380	1.36	1429.80	1747	17.3	−87.9	19.1	lateral occipital
Surface area	left	n.s.							
	right	n.s.							
Thickness	left	0.00050	2.3	1557.03	2006	−23.7	−93.2	−15.5	lateral occipital
	right	n.s.							
CON vs. RISK-T									
Volume	left	n.s.							
	right	n.s.							
Surface area	left	n.s.							
	right	n.s.							
Thickness	left	0.00180	2.03	1258.83	1623	−22.5	−93.9	−15.8	lateral occipital
	right	0.00370	1.52	1165.63	1407	9.8	−98.1	9.2	cuneus
CON vs. RISK-NT									
Volume	left	n.s.							
	right	n.s.							
Surface area	left	0.02560	−0.75	1304.15	1685	−40.8	−9.3	−42.7	inferior temporal
	right	n.s.							
Thickness	left	n.s.							
	right	n.s.							

S2.2 Additional analysis: Morphological differences when controlling for chlorpromazine (CPZ) equivalents

Because some of the subjects in the at risk state were treated with antipsychotics (Table 1), we wanted to test whether our results are influenced by this treatment. Therefore, we included calculated chlorpromazine (CPZ) equivalents as a nuisance variable. This additional analysis revealed that the reported results were not driven by antipsychotic treatments.

Figure S2.2.1: Differences in BS vs. UHR when controlling for chlorpromazine (CPZ) equivalents

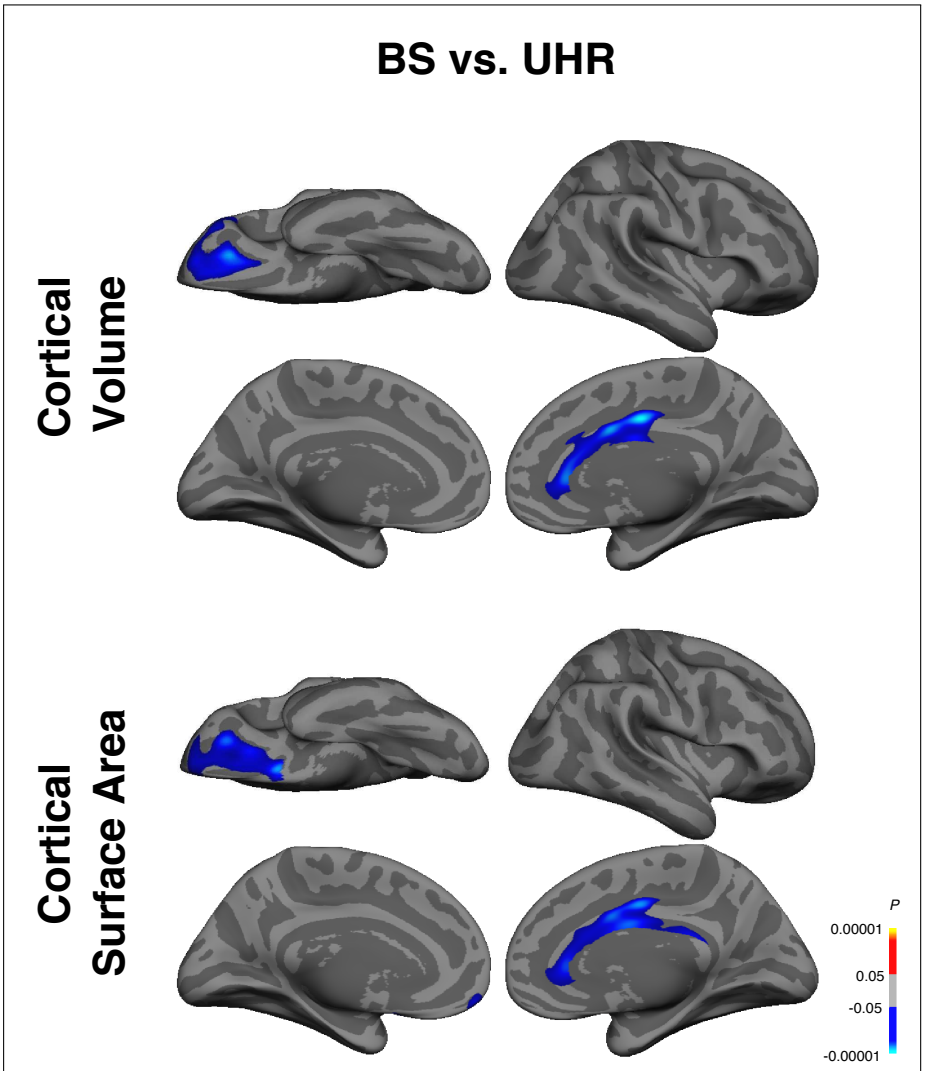


Figure S2.2.1. Differences in cortical volume and surface area when controlling for chlorpromazine (CPZ) equivalents in subjects presenting basic symptoms (BS) compared to individuals at ultra-high risk (UHR). Colored highlights show areas of significant different cortical volume and cortical surface area ($p < .05$, two-tailed, corrected for multiple comparisons); red would indicate a smaller volume/surface area in UHR subjects, while blue stands for regions with greater volume/surface area in UHR compared to BS subjects.

Figure S2.2.2: Differences in RISK-T vs. RISK-NT when controlling for chlorpromazine (CPZ) equivalents

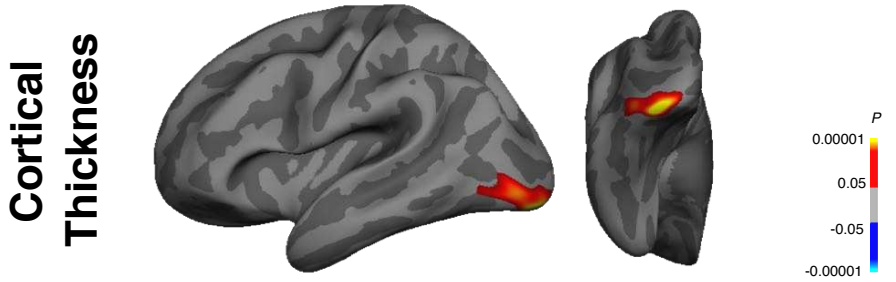


Figure S2.2.2. Differences in cortical thickness when controlling for chlorpromazine (CPZ) equivalents in at-risk subjects grouped according to their clinical outcome, i. e. subjects who later developed psychosis (RISK-T) vs. those who did not (RISK-NT). Only one cluster survived the correction for multiple comparisons pictured on the lateral (left) and the caudal/inferior (right) view of the left hemisphere. Colored highlights show areas of significant different cortical thickness ($p < .05$, two-tailed, corrected for multiple comparisons); red indicates increased values in the first group of the comparison, while blue shows regions with increased values in the second group of the comparison.

Table S2.2.1: Clusters of morphological differences when controlling for chlorpromazine (CPZ) equzivalents

Vertex-wise tests controlling for chlorpromazine equivalents

Measurement	Hemisphere	CWP	Effect Size Cohen's d	Cluster Size (mm^2)	Number of Vertices	MNI coordinates			Structure
						x	y	z	
Posthoc t-tests									
BS vs. UHR									
Volume	left	0.00080	−0.82	1770.70	2043	−22.4	33.2	−10.0	lateral orbitofrontal
		0.02460	−0.72	1113.04	1272	−34.0	48.6	19.6	rostral middle frontal
	right	0.00500	−0.91	1375.96	2888	6.8	−8.1	38.8	posterior cingulate
Surface area	left	0.00120	−0.74	1896.18	2338	−10.1	11.3	−14.9	orbitofrontal
	right	0.01340	−0.84	1416.88	3010	7.5	−8.0	39.0	posterior cingulate
Thickness	left	n.s.							
	right	n.s.							
RISK-NT vs. RISK-T									
Volume	left	n.s.							
	right	n.s.							
Surface area	left	n.s.							
	right	n.s.							
Thickness	left	0.00010	1.52	1573.56	2023	−24.9	−91.6	−15.2	lateral occipital
	right	n.s.							

S2.3 Additional analysis: Correlation with symptoms

Correlations were tested between the morphometric values (cortical surface area or cortical thickness, respectively) and the symptoms (SIPS positive, COPER sum score, COGDIS sum score). The morphometric values stem from significant clusters revealed by comparing the group regarding CSA (or CT, respectively).

Table S2.3.1: Correlation between clusters with morphometric differences and positive symptoms

Cluster	Correlation Coefficient Rho	*P*
Correlation in UHR		
Surface Area Left Orbitofrontal (CSA difference BS vs. UHR)	0.21	.1929
Surface Area Right Posterior Cingulate (CSA difference BS vs. UHR)	0.08	.6124
Surface Area Left Orbitofrontal (CSA difference CON vs. UHR)	0.23	.1647
Surface Area Left Lateral Occipital (CSA difference CON vs. UHR)	0.07	.6578
Surface Area Right Superior Parietal (CSA difference CON vs. UHR)	-0.01	.9755
Correlation in RISK-T		
Thickness Left Lateral Occipital (CT difference RISK-NT vs. RISK-T)	0.35	.3161

Table S2.3.2: Correlation between clusters with morphometric differences and COPER sum score

Cluster	Correlation Coefficient Rho	*P*
Correlation in UHR		
Surface Area Left Orbitofrontal (CSA difference BS vs. UHR)	-0.23	.1589
Surface Area Right Posterior Cingulate (CSA difference BS vs. UHR)	0.02	.8899
Surface Area Left Orbitofrontal (CSA difference CON vs. UHR)	-0.17	.29
Surface Area Left Lateral Occipital (CSA difference CON vs. UHR)	-0.17	.2995
Surface Area Right Superior Parietal (CSA difference CON vs. UHR)	-0.27	.1015
Correlation in RISK-T		
Thickness Left Lateral Occipital (CT difference RISK-NT vs. RISK-T)	-0.40	.2552
Correlation in RISK (BS and UHR)		
Surface Area Left Orbitofrontal (CSA difference BS vs. UHR)	0.06	.5774
Surface Area Right Posterior Cingulate (CSA difference BS vs. UHR)	0.17	.1163
Surface Area Left Orbitofrontal (CSA difference CON vs. UHR)	0.07	.5194
Surface Area Left Lateral Occipital (CSA difference CON vs. UHR)	-0.00	.9982
Surface Area Right Superior Parietal (CSA difference CON vs. UHR)	-0.05	.6397

Table S2.3.3: Correlation between clusters with morphometric differences and COGDIS sum score

Cluster	Correlation Coefficient Rho	*P*
Correlation in UHR		
Surface Area Left Orbitofrontal (CSA difference BS vs. UHR)	-0.31	.0542
Surface Area Right Posterior Cingulate (CSA difference BS vs. UHR)	-0.09	.5765
Surface Area Left Orbitofrontal (CSA difference CON vs. UHR)	-0.22	.1769
Surface Area Left Lateral Occipital (CSA difference CON vs. UHR)	-0.25	.1263
Surface Area Right Superior Parietal (CSA difference CON vs. UHR)	-0.18	.2726
Correlation in RISK-T		
Thickness Left Lateral Occipital (CT difference RISK-NT vs. RISK-T)	-0.26	.4697
Correlation in RISK (BS and UHR)		
Surface Area Left Orbitofrontal (CSA difference BS vs. UHR)	-0.03	.7930
Surface Area Right Posterior Cingulate (CSA difference BS vs. UHR)	0.08	.4511
Surface Area Left Orbitofrontal (CSA difference CON vs. UHR)	-0.02	.8520
Surface Area Left Lateral Occipital (CSA difference CON vs. UHR)	-0.02	.8239
Surface Area Right Superior Parietal (CSA difference CON vs. UHR)	0.02	.8512

S2.4 Additional analysis: Morphological differences in BS subjects meeting COGDIS criterion

Upon request of a reviewer, we additionally performed the analysis with a modified BS group. Specifically, we excluded BS subjects (n=14) who only met the COPER criterion but not the COGDIS criterion. Hence, each BS subject in this additional analysis fulfilled the COGDIS criterion (n=32) while the CON (n=34) and UHR (n=39) groups remained the unchanged. As shown in Figure S2.4.1 and Table S2.4.1, the results did not differ substantially.

Figure S2.4.1: Morphological differences in BS subjects meeting COGDIS criterion

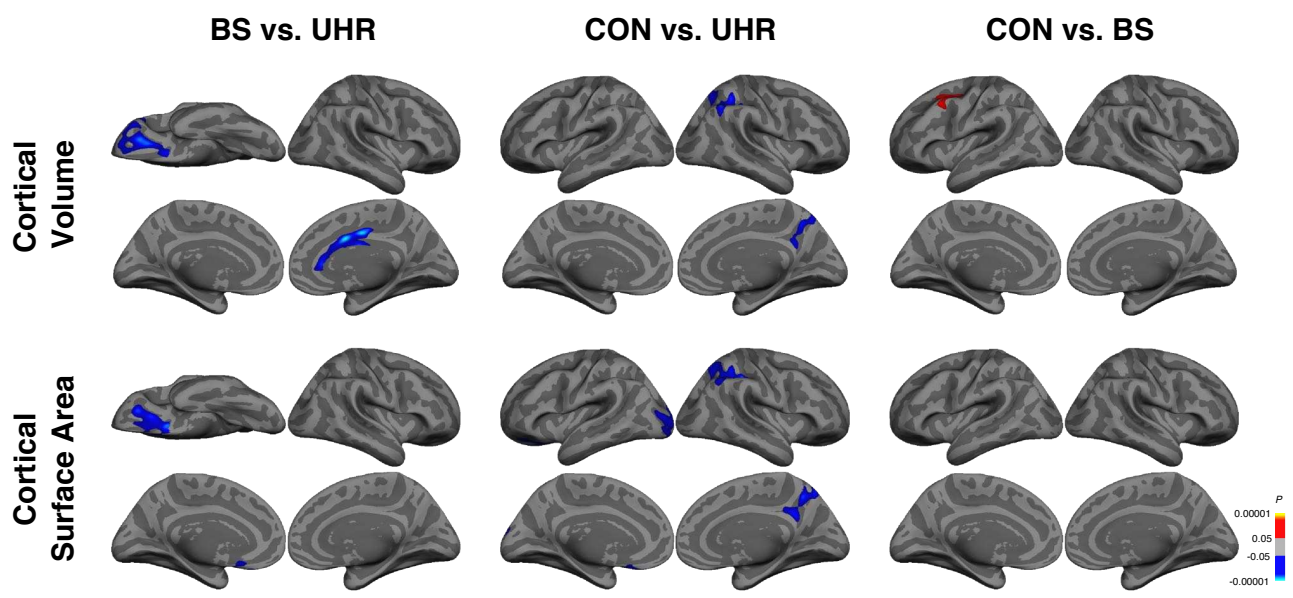


Figure S2.4.1. Morphometric differences when BS subjects who fulfill COGDIS were compared to CON and UHR. Colored highlights show areas of significant differences (cluster-wise threshold set at $p < .05$, two-tailed, Monte Carlo simulations); red indicates greater values in the first group, while blue would show regions with greater values in the second group of the comparison.

Table S2.4.1: Clusters of morphological differences in BS subjects meeting COGDIS criterion

Vertex-wise tests BS subjects meeting COGDIS criterion (CON vs. $BS_{[COGDIS]}$ vs. UHR)

Measurement	Hemisphere	CWP	Effect Size Cohen's d	Cluster Size (mm^2)	Number of Vertices	MNI coordinates			Structure
						x	y	z	
Posthoc t-tests									
$BS_{[COGDIS]}$ vs. UHR									
Volume	left	0.00010	−0.93	2573.91	3044	−32.8	48.1	20.4	rostral middle frontal
		0.00150	−0.78	1587.98	1879	−22.4	33.2	−10.0	lateral orbitofrontal
	right	0.02370	−0.92	1096.41	2357	4.7	9.2	33.8	caudal anterior cingulate
Surface area	left	0.02970	−0.76	1222.34	1696	−10.5	11.5	−14.5	orbitofrontal
		0.00050	−0.85	1995.42	2286	−32.8	48.1	20.4	rostral middle frontal
	right	n.s.							
Thickness	left	n.s.							
	right	n.s.							
CON vs. $BS_{[COGDIS]}$									
Volume	left	0.04690	−0.39	981.61	1516	−27.9	9.8	49.3	caudal middle frontal
	right	n.s.							
Surface area	left	n.s.							
	right	n.s.							
Thickness	left	n.s.							
	right	n.s.							

S2.5 Additional analysis: Group-by-age interaction CON vs. UHR volume

On demand of a reviewer, a group-by-age interaction analysis between CON and UHR groups was conducted. This analysis revealed a significantly different age slope in the left dorsolateral frontal cortex between these groups.

Figure S2.5.1: Group-by-age interaction CON vs. UHR volume

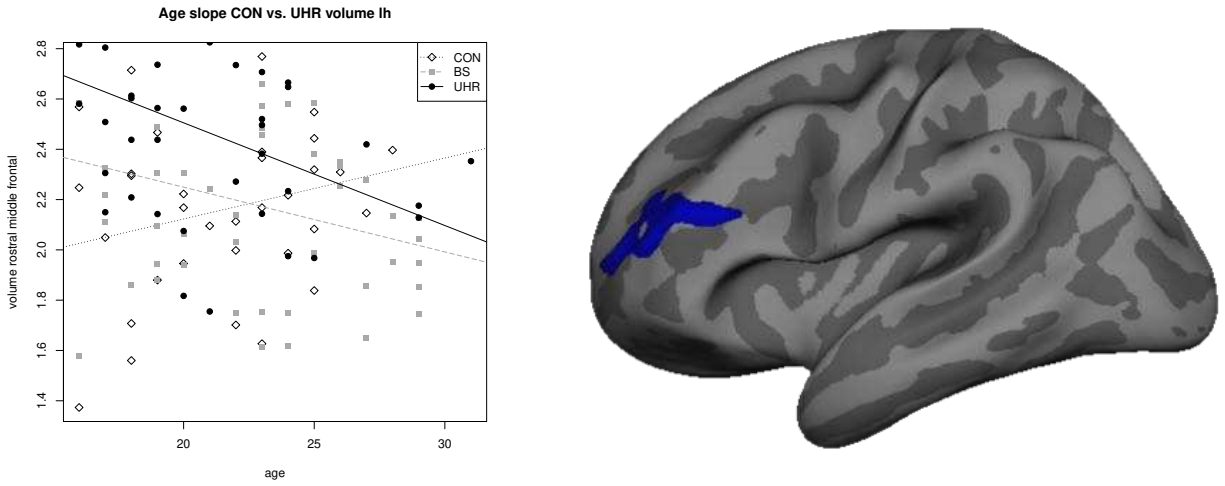


Figure S2.5.1. Group-by-age interaction in CON vs. UHR. Colored highlights show areas of significant different age slope between groups (cluster-wise threshold set at $p < .05$, two-tailed, Monte Carlo simulations); red would indicate greater values in the first group, while blue shows regions with greater values in the second group of the comparison. The scatter plot shows the different slopes in this significant cluster for each group

S2.6 Additional analysis: Whole-brain correlation analyses

As requested by a reviewer, the association with symptoms (COPER sum score, COGDIS sum score, SIPS positive score, SIPS negative score) was tested among the whole RISK group (i. e. BS and UHR) and across the whole cortex.

S2.6.1 Correlation with COPER (sum score)

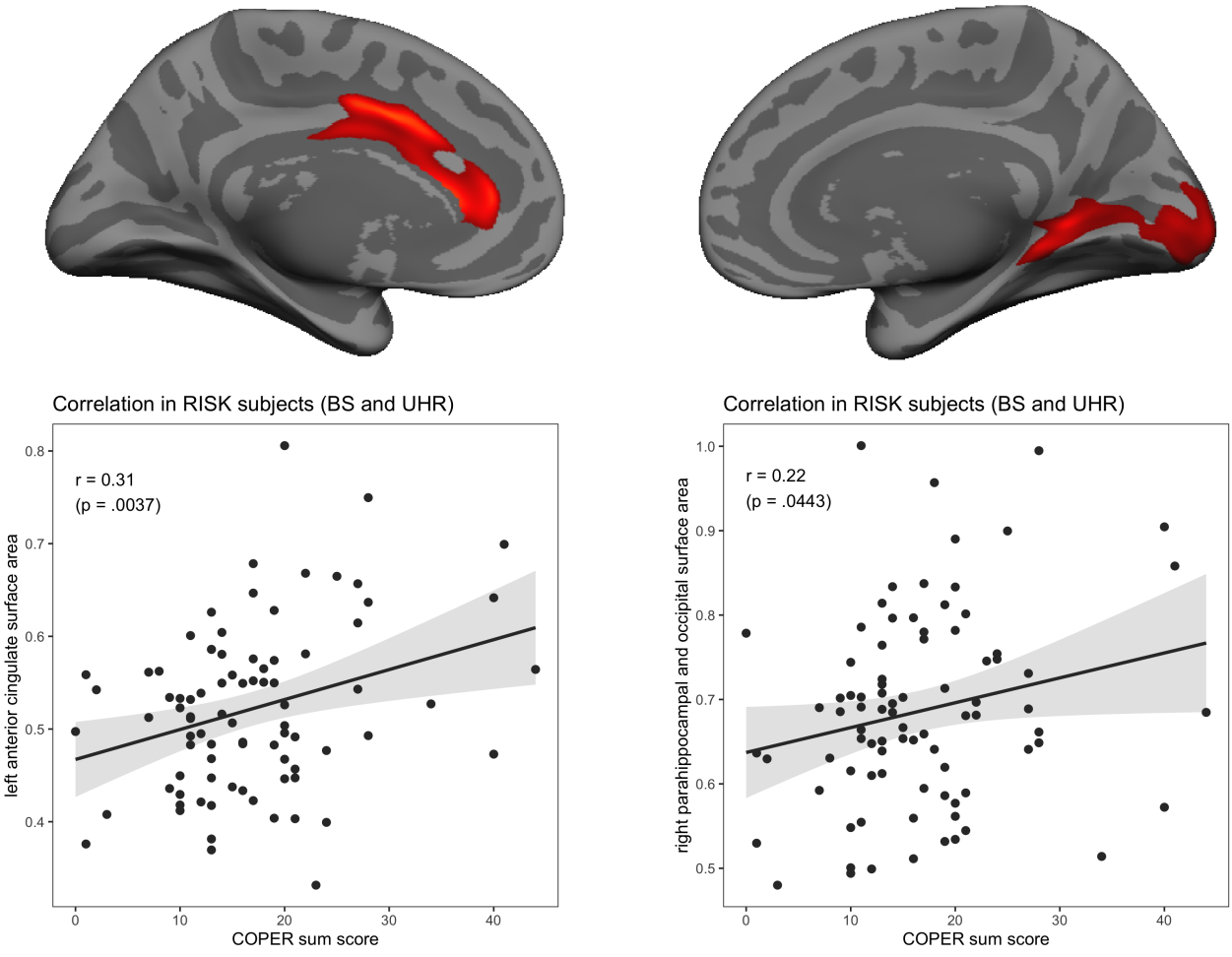


Figure S2.6.1. Correlation between surface area and COPER sum score. Colored highlights show areas of significant correlations (cluster-wise threshold set at $p < .05$, two-tailed, Monte Carlo simulations); red indicates a positive correlation, while blue would show regions with negative correaltions.

S2.6.2 Correlation with COGDIS (sum score)

No clusters with significant correlations between surface area and COGDIS sum score were found in RISK subjects (BS and UHR groups together).

S2.6.3 Correlation with positive Symptoms (SIPS positive score)

Figure S2.6.3a: Group-by-age interaction CON vs. UHR volume

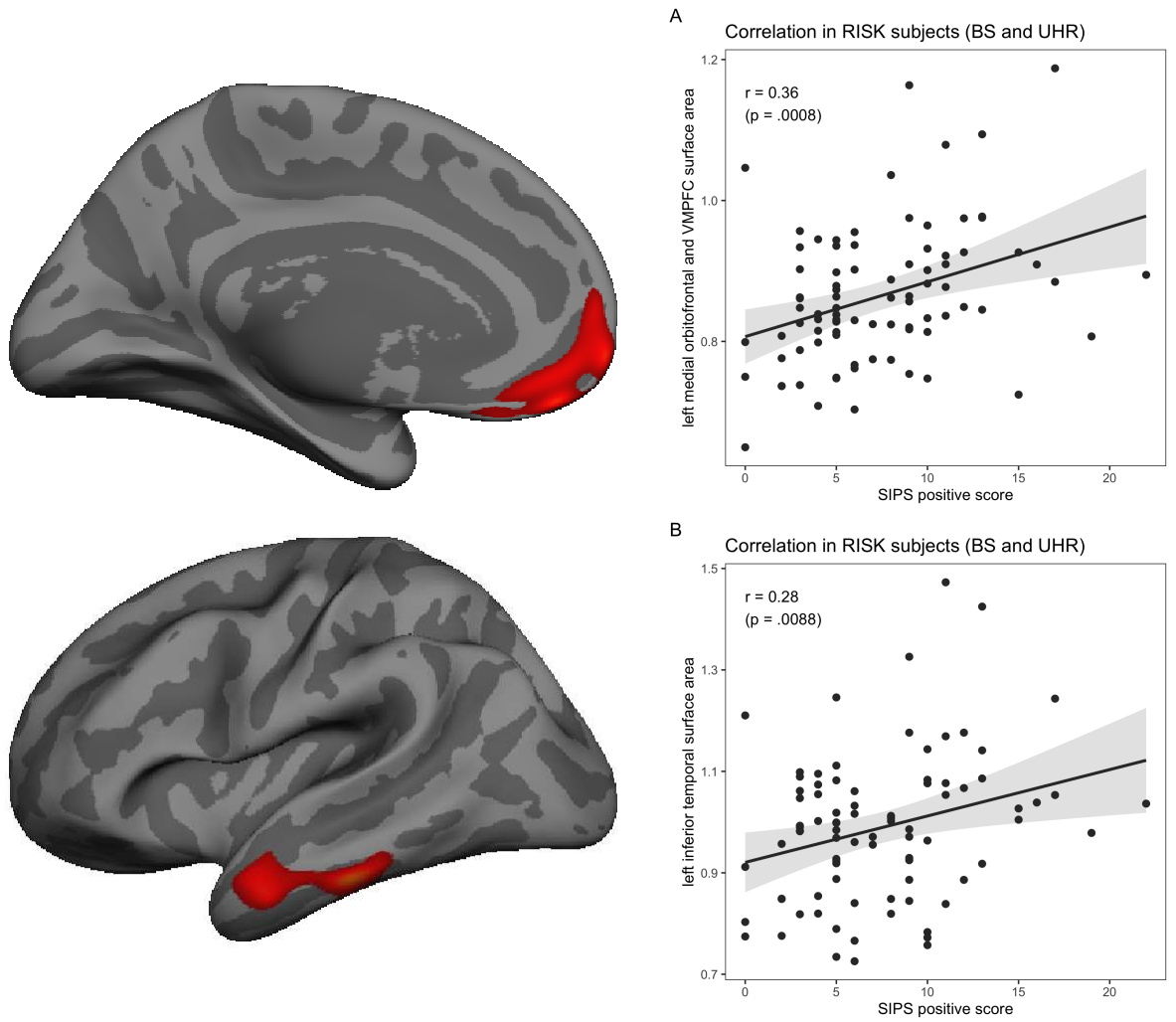


Figure S2.6.3a. Correlation between surface area and SIPS positive score. Colored highlights show areas of significant correlations (cluster-wise threshold set at $p < .05$, two-tailed, Monte Carlo simulations); red indicates a positive correlation, while blue would show regions with negative correaltions.

The cluster shown in the upper panel (A) is overlapping with one of the significant clusters of group differences in BS vs. UHR (see Figure 1 and Table 1). Hence, there is a chance that this correlation might evolve because of group differences in surface area and SIPS positive score (one group with low values in both variables combined with the second group presenting high values in both variables). In order to elucidate the associations between the positive symptoms and surface area in each group, we additionally tested the correlation group-wise and plotted (Figure S2.6.3b) the results for each group separately. As shown in Table S2.6.3b, the correlation is driven by BS subjects.

Table S2.6.3b: Correlation left medial orbitofrontal and VMPFC surface area with SIPS positive score

Group	Correlation Coefficient Rho	*P*
Correlation in RISK (BS and UHR)	0.37	.0005
Correlation within BS group	0.32	.0298
Correlation within UHR group	0.21	.1925

Figure S2.6.3b: Correlation with SIPS positive score

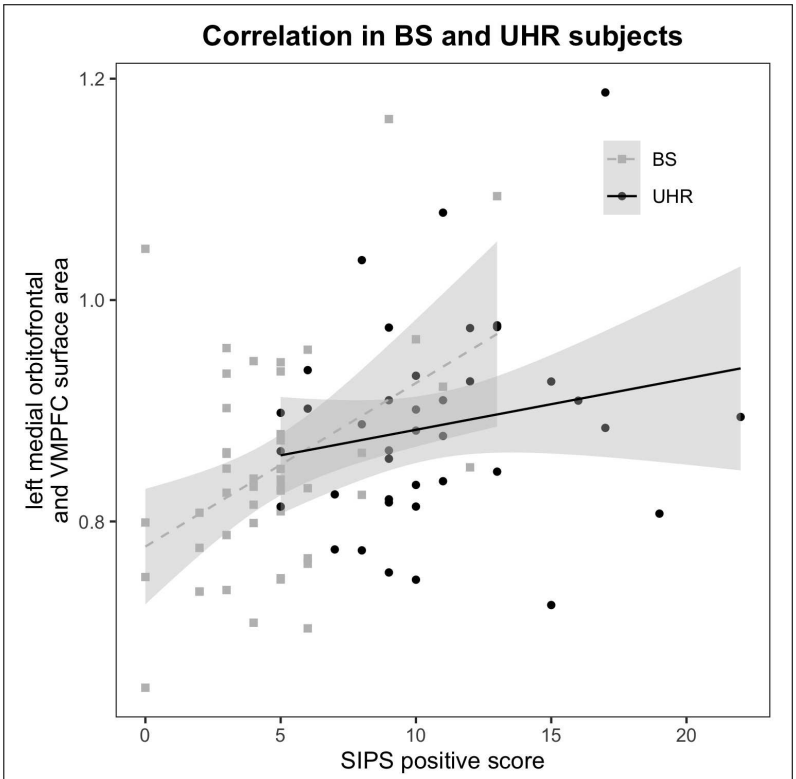


Figure S2.6.3b: Correlation between surface area and SIPS positive score within the BS and UHR groups respectively.

S2.6.4 Correlation with negative Symptoms (SIPS negative score)

No clusters with significant correlations between surface area and SIPS negative score were found in RISK subjects (BS and UHR groups together).

References

[1] Schultze-Lutter F, Addington J, Ruhrmann S, Klosterkötter J. Schizophrenia Proneness Instrument, Adult version (SPI-A). Editore s r l GF, editor. Rome, Italy; 2007.

[2] Fux L, Walger P, Schimmelmann BG, Schultze-Lutter F. The Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY): practicability and discriminative validity. Schizophrenia Research. 2013 may;146(1-3):69–78. Available from: http://dx.doi.org/10.1016/j.schres.2013.02.014.

[3] Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin. 2003;29(4):703–715. Available from: http://dx.doi.org/10.1093/oxfordjournals.schbul.a007040.

[4] McGlashan T, Miller T, Woods S, Rosen J, Hoffman R, Davidson L, et al. Structured interview for prodromal syndromes. New Haven, CT: PRIME Research Clinic, Yale School of Medicine. 2001;.

[5] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin. 1987;13(2):261–276. Available from: http://dx.doi.org/10.1093/schbul/13.2.261.

[6] Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. Journal of Affective Disorders. 2005 oct;88(2):217–233. Available from: http://dx.doi.org/10.1016/j.jad.2005.05.011.

[7] Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. The British Journal of Psychiatry Supplement. 1993 dec;(22):39–44. Available from: http://dx.doi.org/10.1192/S0007125000292581.

[8] Hamilton M. A RATING SCALE FOR DEPRESSION. Journal of Neurology, Neurosurgery & Psychiatry. 1960;23(1):56–62. Available from: https://jnnp.bmj.com/content/23/1/56.

[9] Steer R, Beck A, Zalaquett C. Beck anxiety inventory. In: Richard JW, editor. Evaluating Stress: A Book of Resources. vol. xvii. Lanham, MD: Scarcrow Education; 1997. p. 23–40.

[10] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of Clinical Psychiatry. 1998;59 Suppl 20:22–33. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9881538.

[11] McGlashan T, Miller TJ, Woods SW, Rosen JL, Hoffman RE, Davidson L. Structured interview for prodromal syndromes - version for present prodromal syndromes. New Haven, Connecticut: PRIME Research Clinic, Yale School of Medicine; 2001.

[12] Organization WH. The Icd-10 Classification Of Mental And Behavioural Disorders: Clinical Descriptions And Diagnostic Guidelines. 1st ed. Geneva: World Health Organization; 1992.

[13] Theodoridou A, Heekeren K, Dvorsky D, Metzler S, Franscini M, Haker H, et al. Early recognition of high risk of bipolar disorder and psychosis: an overview of the zinep "early recognition" study. Frontiers in public health. 2014 oct;2:166. Available from: http://dx.doi.org/10.3389/fpubh.2014.00166.

[14] Rimol LM, Nesvåg R, Hagler DJ, Bergmann O, Fennema-Notestine C, Hartberg CB, et al. Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. Biological Psychiatry. 2012 mar;71(6):552–560. Available from: http://dx.doi.org/10.1016/j.biopsych.2011.11.026.

[15] Calhoun VD, Sui J, Kiehl K, Turner J, Allen E, Pearlson G. Exploring the psychosis functional connectome: aberrant intrinsic networks in schizophrenia and bipolar disorder. Frontiers in psychiatry. 2011;2:75. Available from: http://dx.doi.org/10.3389/fpsyt.2011.00075.

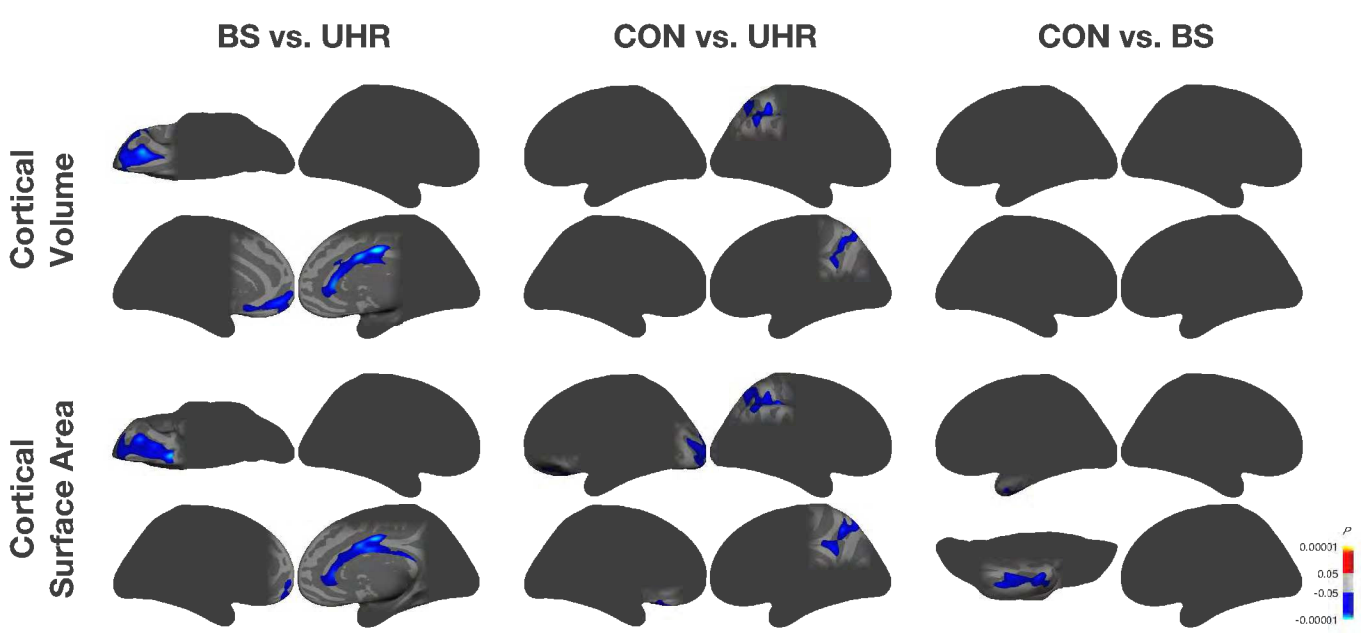
[16] de Zwarte SMC, Brouwer RM, Agartz I, Alda M, Aleman A, Alpert KI, et al. The Association Between Familial Risk and Brain Abnormalities Is Disease Specific: An ENIGMA-Relatives Study of Schizophrenia and Bipolar Disorder. Biological Psychiatry. 2019 oct;86(7):545–556. Available from: http://dx.doi.org/10.1016/j.biopsych.2019.03.985.

Table 1

Characteristics of subjects assigned to three test groups.

	CON	BS	UHR	Statistics		
	(n=34)	(n=46)	(n=39)	F,χ^2,U	p	Cohen's d
Age in years [m±sd]	21.76±3.73	22.7±4.03	21.79±4.71	F=0.6752	0.5111	
-range	16−31	16−29	16−35			
Sex male/female (%male)	16/18 (47%)	23/23 (50%)	25/14 (64%)	χ^2=2.5541	0.2789	
Handedness r/a/l (%left)	27/3/4 (12%)	42/2/2 (4%)	36/0/3 (8%)	χ^2=5.2152	0.2659	
Estimated IQ [m±sd]	112.13±13.68	105.91±11.49	107.25±14.34	F=2.3149	0.1034	
COPER sum score [m±sd]	NA	14.61±5.43	19.33±10.7	U=636.5	0.0216	-0.56
COGDIS sum score [m±sd]	NA	11.76±6.45	14.67±8.67	U=711	0.1014	
SIPS Positive score [m±sd]	NA	4.67±2.93	10.67±3.89	U=170.5	<.001	-1.74
SIPS Negative score [m±sd]	NA	11.24±5.85	13.59±5.79	U=689.5	0.0675	
SIPS General [m±sd]	NA	7.28±3.42	8.9±3.68	U=633.5	0.0197	-0.46
SIPS Disorganization [m±sd]	NA	2.93±1.87	5.08±2.58	U=454	<.001	-0.95
GAF [m±sd]	NA	57.98±16.4	50.33±12.68	U=1121	0.0087	0.52
Chlorpromazine [m±sd]	NA	21.66±63.01	40.33±101.7	U=781	0.1706	
Transition (3-year follow-up, mean = 12.2 months)						
to F20	NA	3 (RISK-T)	7 (RISK-T)			
to F23/BPD I	NA	2 F23	1 F23/1 BPD			

Abbreviations: CON, control group; BS, basic symptoms group; UHR, ultra-high risk group; m, mean; sd, standard deviation; r, right; a, ambidextrous; l, left; COPER, cognitive-perceptive basic symptoms; COGDIS, cognitive disturbances; SPIA, Schizophrenia Proneness Instrument Adult Version; SIPS, Structured Interview for Psychosis-Risk Syndromes; GAF, global assessment of functioning; CPZ, chlorpromazine; F, ANOVA F test; χ^2, Chi-square test; U, Mann-Whitney U test; BPD, Bipolar I disorder; F23, Acute and transient psychotic disorders according to ICD-10.


BS vs. UHR
CON vs. UHR
CON vs. BS
Cortical Volume
Cortical Surface Area
P
0.00001
0.05
-0.35
-0.00001

RISK-NT vs. RISK-T

Cortical Thickness